Myelodysplastic Syndromes: Current Thinking on the Disease, Diagnosis and Treatment

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Aplastic Anemia & MDS International Foundation
Regional Patient and Family Conference
July 18th, 2015

Overview

- Introduction to MDS
- Pathophysiology
- Clinical Practice
  - Making the diagnosis
  - Risk stratification
  - Selecting therapy
- Future Directions/Challenges

Low Blood Counts

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

Shared features:
- Ineffective differentiation and low blood counts
- Clonal expansion of abnormal cells
- Risk of transformation to acute leukemia

Afflicts 15,000 – 45,000 people annually

Incidence rises with age (mean age 71)

Myelodysplastic Syndromes

MDS Incidence Rates 2000-2008

US SEER Cancer Registry Data

Age and Sex in MDS

Overall incidence in this analysis: 3.4 per 100,000

*P for trend < .05

Slide borrowed from Dr. David Steensma
Rollison DE et al Blood 2008;112:45-52.
**Etiology of MDS**

- **<2%** Familial or Congenital
- **10-15%** "De novo" (idiopathic, primary)
- **85%** Topoisomerase II inhibitors, Ionizing radiation, DNA alkylating agents

Often early onset and part of a larger syndrome

Peaks 1-3 or 5-7 years following exposure

Median age ~71 years; increased risk with aging

**Risk factors for MDS**

- **Environmental**
  - AGING
  - Exposure to DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide)
  - Exposure to topoisomerase II inhibitors (etoposide, anthracyclines)
  - Exposure to ionizing radiation
  - Environmental / occupational exposures (hydrocarbons etc.)
  - Antecedent acquired hematological disorders
    - Aplastic anemia (15-20%)
    - PNH (5-25%)

- **Inborn**
  - Fanconi anemia
  - Familial Platelet Disorder with AML Predisposition ("FPD-AML") (RUNX1, GATA2 mutant)
  - Other congenital marrow failure syndromes or DNA repair defects (Bloom syndrome, ataxia-telangiectasia, etc.)
  - Familial syndromes of unknown origin

**Corrupted Hematopoiesis**

**Differentiation**

**Transformation**

**Making the Diagnosis**

**Diagnostic Overlap**
Myelodysplastic Syndromes

Diagnosis of MDS is largely MORPHOLOGIC, so you need is:

- Bone Marrow Aspirate/Biopsy
- Complete Blood Count with white cell differential
- Karyotype (chromosome analysis)

Sometimes useful:

- MDS FISH panel – usually if karyotype fails
- Flow cytometry – aberrant immunophenotype
- Genetic Testing – may become standard eventually

Cytopenia(s), suspect myelodysplasia:

- Anemia
- Thrombocytopenia
- Leukopenia

Minimum Evaluation Needed

MDS “decisive” criteria:

- >10% dysplastic cells in 1 or more lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Evidence of clonality (by FISH or another test)

Other causes of cytopenias and morphological changes EXCLUDED:

- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)

Minimal Diagnostic Criteria

Diagnostic Overlap

Bone Marrow Biopsy

Looking for Answers

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

B12 level - Normal
Folate - Normal
Thyroid - Normal
No toxic medications
No alcohol use
No chronic illness
65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**
Refractory cytopenia with unilineage dysplasia

**WHO Prognostic Scoring System**

<table>
<thead>
<tr>
<th>WPSS Parameter</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
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</thead>
<tbody>
<tr>
<td>WHO Category</td>
<td>0</td>
<td>20%</td>
<td>9-11</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20%</td>
<td>5-6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>20%</td>
<td>4.5-5.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>20%</td>
<td>3.5-4.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>20%</td>
<td>2.0-2.5</td>
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</tbody>
</table>

*Median survival ranges for the WPSS were estimated from Malcovati et al. Haematologica. 2011 Oct;96(10):1433-40.*

**International Prognostic Scoring System**

**IPSS-Revised (IPSS-R)**

**MDS Risk Assessment**

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**
Refractory cytopenia with unilineage dysplasia

**Risk Adapted Therapy**

WPSS – Very Low Risk
IPSS – Low Risk
IPSS-R - Very Low Risk
Treatment Options for MDS

Observation
- Erythropoiesis stimulating agents
- Granulocyte colony stimulating factor
- Iron chelation
- Red blood cell transfusion
- Platelet transfusion
- Lenalidomide
- Immune Suppression
- Hypomethylating agent
- Stem cell transplantation

Clinical Trials – always the best option

MDS Risk Assessment

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WPSS - Very Low Risk
IPSS - Low Risk
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Clinical Trials – always the best option

Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

1. Do I need to treat at all?
   - No advantage to early aggressive treatment
   - Observation is often the best approach

2. Are transfusions treatment?
   - No! They are a sign that treatment is needed.

Guidelines for Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

What if treatment is needed?

1. Is my most effective therapy likely to work?
   - Lenalidomide (Revlimid)
   - In del(5q) – response rates are high
   - 50%-70% respond to treatment
   - Median 2-years transfusion free!

Treating Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE

Is my second most effective therapy likely to work?

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
- Darbepoetin alfa (Aranesp)
- Epoetin alfa (Procrit, Epogen)
- Lance Armstrong Juice ➔ EPO
**Erythropoiesis Stimulating Agents**

**Primary Goal:** to improve QUALITY OF LIFE

ESAs – act like our own erythropoietin

<table>
<thead>
<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC transfusion requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>+2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>+1 pt</td>
</tr>
<tr>
<td>&gt;500</td>
<td>-3 pts</td>
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</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of response: &gt; +1</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>Intermediate likelihood: -1 to +1</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>Low likelihood of response: &lt; -1</td>
<td>7% (n=39)</td>
</tr>
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</table>

**Growth Factor Combinations**

**Primary Goal:** to improve QUALITY OF LIFE

ESAs – act like our own TPO mimetics

**Thrombopoietin Mimetics**

**Primary Goal:** to improve QUALITY OF LIFE

Eltrombopag and Romiplostim – approved, but not in MDS

Initial concern about increasing blasts and risk of AML

Follow-up suggests Romiplostim safe in lower risk patients

**Treating Lower Risk MDS**

**Primary Goal:** to improve QUALITY OF LIFE

What my next most effective therapy?

- Immunosuppression

Some MDS patients have features of aplastic anemia

- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)

**Immune Suppression for MDS**

**Primary Goal:** to improve QUALITY OF LIFE

Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)

Mostly men with Lower Risk MDS

CR+PR: 29% vs. 9%

No effect on survival

Predictors of Response:
- hypocellular aspirate
- lower aspirate blast %
- younger age
- more recent diagnosis

**Hypomethylating Agents**

Inhibitors of DNA methyl transferases:

**Immune Suppression for MDS**

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**Hypomethylating Agents**

Inhibitors of DNA methyl transferases:
Iron Balance and Transfusions

Daily intake
1.5 mg (0.04%)
Tightly regulated

Daily losses only
1.5 mg (0.04%)
Not regulated!

3-4 grams of Iron
in the body

Every three
units of blood

What About Iron Chelation?

More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

Are these drivers of prognosis or just reflective of disease?

Retrospective studies suggest survival advantage!

small prospective and large population based Medicare studies show survival benefit, INCLUDING hematologic responses (11-19%).

I consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.


How to Chelate Iron

Three ways are FDA approved:
Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
Deferasirox (Exjade) – oral suspension – once per day
Deferiprone (Ferriprox) – oral pill form – 3x per day

But side effects and adverse events can be significant!
Deferasirox – renal, hepatic failure and GI bleeding
Deferiprone – agranulocytosis (no neutrophils!)

Guidelines for Lower Risk MDS

Primary Goal: to improve QUALITY OF LIFE
1. Do I need to treat? - symptomatic cytopenias
2. Is LEN likely to work? - del(5q) ±
3. Are ESA likely to work? - Serum EPO < 500
4. Is IST likely to work? - hypocellular, DR15, PNH
5. Think about iron! - 20 or more transfusions
6. Consider AZA/DEC
7. Consider HSCT or clinical trial!

Guidelines for Lower Risk MDS

Special Considerations:

Transfusion Dependence
- Indication for treatment – even with AZA/DEC, consider chelation

Del(5q)
- High response rate to LEN even if other abnormalities

Serum EPO level
- Used to predict EPO response, > 500 → unlikely to work

Indication for G-CSF
- used to boost EPO, not for primary neutropenia

Immunosuppressive Therapy
- ≤ 60y, hypocellular marrow, HLA-DR15+, PNH clone

Future Directions
Limitations of the IPSS/IPSS-R

- Less than half of patients have relevant cytogenetic abnormalities
- Heterogeneity remains within each risk category, particularly the lower-risk categories
- Excludes therapy related disease and CMML
- Is only validated at the time of initial diagnosis in untreated patients

The IPSS's do not include molecular abnormalities

TP53 Mutations and Complex Karyotypes

The adverse prognostic impact of the complex karyotype is entirely driven by its frequent association with mutations of TP53

Impact of Mutations by IPSS Group

Tracking the Founder Clone

Clonal Evolution

Mutation Frequency and Distribution